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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
EWOLDT, GERALD R	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte LOUIS D. FALO, JR. and CHRISTINA M. CELLUZZI

Appeal 2008-4549[1]
Application 10/608,424
Technology Center 1600

Decided:[2] February 26, 2009

Before TONI R. SCHEINER, DONALD E. ADAMS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The real party in interest is the University of Pittsburgh.

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 2, and 4-12, all the claims pending in the application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

> Tumor cells and virally infected cells express antigens which can be targeted by CTLs [cytotoxic T lymphocytes], but the tumor cells and virally infected cells themselves do not stimulate CTL immunity. This is presumably because the tumor cells and viral cells are incapable of providing the antigen or antigens in the appropriate context of co-stimulation. Antigen presenting cells (APC), however, express a variety of co-stimulatory molecules and cytokines. The present invention provides formulations in which APCs are fused to or are in a co-culture with either tumor cells or virally infected cells. The fused cells and/or co-cultured cells are then used to provide a complete array of tumor antigens or viral antigens that can be delivered to the endogenous pathway of APCs from MHC Class I specific presentation and CTL stimulation. Fusion or co-culture of the APCs with the tumor cells or virally infected cells causes the tumor antigens to become more immunogenic by association with the professional APCs. The fusion products and the co-culture products express properties of both the APC and the tumor; these products are capable of priming a CTL response.

(Spec. 4: 5-19.)

The present invention is directed to "a formulation comprising hybridomas of antigen presenting cells fused to . . . virally infected cells" (Spec. 1: 5-7).

Claims 1, 4, and 8 are representative of the subject matter on appeal:

1. A formulation comprising at least one hybridoma having at least one first cell fused to at least one second cell;

wherein said first cell is an antigen presenting cell selected from the group consisting of a macrophage and a dendritic cell, and said second cell is a virally infected cell.

4. The formulation of claim 1, wherein said virally infected cells are selected from the group consisting of cells infected with influenza virus, human immunodeficiency virus, cytomegalovirus, human papilloma virus and herpes simplex virus.

8. A pharmaceutical composition comprising: at least one hybridoma; and a suitable pharmaceutical carrier;

wherein each hybridoma is comprised of at least one first cell fused to at least one second cell;

wherein said first cell is an antigen presenting cell selected from the group consisting of a macrophage and a dendritic cell, and said second cell is a virally infected cell.

The Examiner relies on the following evidence:

BASIC & CLINICAL IMMUNOLOGY 697 (Daniel P. Stites et al. eds., Appleton & Lange 6th ed. 1987).

GENES 736 (Benjamin Lewin ed., John Wiley & Sons 3rd ed. 1987).

CHARLES A. JANEWAY, JR. & PAUL TRAVERS, IMMUNOBIOLOGY 2.20-21 (Garland Publishing 1994).

I. Frank & M. Pope, *The Enigma of Dendritic-Cell Immunodeficiency Virus Interplay*, 2 CURRENT MOLECULAR MEDICINE 229-248 (2002).

Josh P. Roberts, *Are HIV Vaccines Fighting Fire with Gasoline?*, 18 THE SCIENTIST 26 (2004).

Appellants rely on the following additional evidence:

Concepción Marañón et al., *Dendritic Cells Cross-Present HIV Antigens from Live as Well as Apoptotic Infected CD4+ T Lymphocytes*, 101 PNAS 6092-6097 (2004).

The Examiner rejected claims 1, 2, and 4-12 under 35 U.S.C. § 112, first paragraph for lack of enablement.

We reverse.

PRINCIPLES OF LAW

"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971) (emphasis in original). "[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* at 224. In other words, "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by [the] claim[s] is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

Moreover, the enablement analysis must be focused on the product or method defined by the claims. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected,

commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). *See also In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims to method of "restoring hair growth" encompassed achieving full head of hair but did not require it). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

Finally, it is well settled that a post-filing publication cannot be used to supplement an insufficient disclose, but can be offered as evidence that a disclosed device would have been operative. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

THE ISSUE

The issue raised by this appeal is whether the Examiner has met his initial burden of setting forth a reasonable explanation as to why it would have required undue experimentation for one skilled in the art to make and use a hybridoma comprising an antigen presenting cell fused to a virally-infected cell.

FINDINGS OF FACT

FF1 Appellants claim a formulation comprising a hybridoma having at least one virally infected cell fused to at least one antigen presenting cell (APC) selected from the group consisting of a macrophage and a dendritic cell.

FF2 According to the Specification, "a hybridoma is a physical combination of at least two different kinds of cells" (Spec. 6: 14-15), and the Specification describes "two different hybridomas . . . namely a hybridoma between at least one APC and one tumor cell; and a hybridoma between at least one APC and at least one virally infected cell" (*id.* at 6: 15-18).

FF3 "In a preferred embodiment, the APC-tumor cell or APC-virally infected cell hybridoma is formed by fusing the two types of cells together with polyethylene glycol (PEG)" (Spec. 8: 4-6).

FF4 The Specification teaches that

> Tumor cells and virally infected cells express antigens which can be targeted by CTLs [cytotoxic T lymphocytes], but the tumor cells and virally infected cells themselves do not stimulate CTL immunity . . . presumably because the tumor cells and viral cells are incapable of providing the antigen or antigens in the appropriate context of co-stimulation. Antigen presenting cells (APC), however, express a variety of co-stimulatory molecules and cytokines.

(Spec. 4: 5-10.)

FF5 According to the Specification,

> [F]ormulations in which APCs are fused to or are in a co-culture with either tumor cells or virally infected cells . . . provide a complete array of tumor antigens or viral antigens that can be delivered to the endogenous pathway of APCs from MHC Class I specific presentation and CTL stimulation. Fusion or co-culture of the APCs with the tumor cells or virally infected cells causes the tumor antigens to become more immunogenic by association with the professional APCs. The fusion products and the co-culture products express properties of both the APC and the tumor; these products are capable of priming a CTL response. This results in the destruction of tumor cells that express similar antigens. Similar results are

> seen when the formulations comprise products using virally-infected cells . . . destruction of the virus.

(Spec. 4: 10-22.)

FF6 The Specification teaches that "the present invention obviates the need to identify specific antigens that elicit a CTL response by providing a mechanism that delivers . . . viral antigens into the MHC [C]lass I restricted antigen processing pathway of professional APCs. By delivering the entire array of antigens produced by . . . a virally infected cell to the APCs, a mechanism is provided for broad, polyvalent immunization" (Spec. 4: 23-28).

FF7 There are no working examples involving fusions or co-cultures of APCs and virally-infected cells in the Specification. However, Examples 1-4 of the present Specification demonstrate that "splenocytes from mice immunized with co-cultures or fusion products of DCs [dendritic cells] and B16 [melanoma cells] lysed B16 targets while splenocytes from mice immunized with co-cultures or fusion products of DCs and 3LL [lung carcinoma cells] lysed 3LL targets" in vitro (Spec. 14: 29-31). That is, lysis was tumor specific (*id.* at 14: 28). "Furthermore, lysis was CD8-T cell mediated as splenocytes depleted for CD8 or Thy 1.2 did not lyse tumor-specific targets" (*id.* at 14: 32-33).

FF8 Example 5 of the present Specification "demonstrate[s] that immunization with products of DC-tumor cell fusions or co-cultures can induce tumor-specific CTLs and potent protective anti-tumor immunity against two distinct, poorly immunogenic tumors" in vivo (Spec. 17: 3-6).

Example 6 demonstrates that the products of DC-3LL fusions or co-cultures induced tumor regression in mice with established tumors (*id.* at 17: 8-23).

FF9 According to Frank,

> A dendritic cell (DC) encountering an immunodeficiency virus should pose a threat to the virus, by efficiently processing and presenting viral antigenic determinants to activate specific anti-viral T and B cell immunity. While this may occur *in vivo*, it is apparent that DC-entrapped viruses can freely spread between cells, move to distal tissues, and proliferate rapidly particularly upon meeting $CD4^+$T cells. In fact, the latter is further augmented when the T cells are activated. Thus, it seems that immunodeficiency viruses exploit the unique ability of DCs to survey the periphery and capture incoming pathogens, traffic around the body often targeting the lymphoid tissues, and efficiently communicate with naïve and memory T cells. Combined with the fact that DCs are likely the first leukocytes interacting with virions crossing the mucosae, these features provide the basis on which the virus maximizes its chance to establish infection even in the face of immune activation.

(Frank, Abstract.)

FF10 On the other hand, Frank also teaches

> While the virus expertly exploits the DC to forge its survival and dissemination, DCs probably also process viral determinants *in vivo*, presenting them to activate (at least low-level) virus-specific immunity . . . Such immune activation likely occurs throughout infection until the immune system ultimately collapses due to the overwhelming virus production and depletion of $CD4^+$ T cells. The extensive capacity of DCs to capture and process antigens via a number of different mechanisms for the activation of $CD4^+$ and $CD8^+$ T cells underscores the potential usefulness of these cells in ensuring activation of broad immune responses . . . However, it is vital that approaches to properly target these pathways be developed

> to capitalize on the DC for vaccine and therapeutic interventions.

(Frank 241, col. 1.)

FF11 Marañón, cited by Appellants as evidence that the "invention works as claimed" (Reply Br. 4), teaches that dendritic cells co-cultured with live, HIV infected $CD4^+$ T cells process and present antigen efficiently (Marañón 6095, col. 2). Marañón suggests that "this HIV antigen presentation pathway could be exploited to eradicate latently infected reservoirs, which are poorly recognized by patients' immune systems" (*id.*, Abstract).

ANALYSIS

The Examiner concluded that the Specification "does not reasonably provide enablement for [making or using] a formulation comprising a hybridoma, said hybridoma comprising a DC [dendritic cell] and a tumor cell" (Ans. 4).

In particular, the Examiner asserts that the Specification is not enabling for making the claimed hybridoma because a hybridoma comprises "'a transformed cell line grown *in vitro* that is a somatic hybrid of 2 parent cell lines'" (Ans. 6[3]), in "'a state of unrestrained growth in culture, resembling or identical with the tumorigenic condition'" (*id.*[4]). The Examiner concludes that the Specification "fails to teach how to make the [dendritic cell - virally infected cell] 'hybridoma' of the instant claims" (*id.*)

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[3] Citing BASIC & CLINICAL IMMUNOLOGY 697.
[4] Citing GENES 736.

because "neither the mortal DC nor the mortal virally-infected cell is capable of contributing transformation/immortality to the claimed formulation" (*id.*).

We do not agree that the term "hybridoma" requires immortalization in the context of the present claims and Specification. Appellants' use of "hybridoma" rather than "hybrid" may be unconventional, but it is clear from the plain language of claim 1 that the claimed hybridoma is simply a virally infected cell fused to a dendritic cell or a macrophage. This interpretation is consistent with the Specification, which differentiates between a possibly immortalized hybridoma "between at least one APC and one tumor cell," and a hybridoma "between at least one APC and at least one virally infected cell" (**FF2**).

The Examiner does not dispute that an antigen presenting cell and a virally infected cell can be physically combined "by fusing the two types of cells together with polyethylene glycol" as taught by the Specification (**FF3**).

We conclude that the Examiner has not met his initial burden of establishing that the Specification would not have enabled one of skill in the art to make the claimed "hybridoma."

The Examiner also asserts that the Specification is not enabling for using the claimed formulations because the "the formulations . . . are pharmaceutical compositions and require enablement as such" (Ans. 4), but the Specification "provides no teachings sufficient to enable claims drawn to a DC hybridoma which induces effective anti-virally-infected cell immunity" (*id.*), especially "in the case of HIV infection" (*id.*).

According to the Examiner, Frank provides evidence "that the formulations of the instant claims would be more likely to exacerbate viral infections than to treat or prevent them" (Ans. 5), at least in part because dendritic cell-entrapped immunodeficiency viruses can be spread to other cells, and can also be transported intact to distal tissues (*id.*).

Nevertheless, despite the ability of immunodeficiency viruses to withstand dendritic cell-entrapment to some degree, Frank teaches that dendritic cells also process and present immunoviral determinants *in vivo* just as they would other viral determinants, activating low level virus-specific immunity in the process. Thus, Frank suggests that the extensive capacity of dendritic cells to capture and process viral antigens via a number of different mechanisms for the activation of $CD4^+$ and $CD8^+$ T cells could be useful in ensuring activation of broad immune responses (**FF10**).

Appellants cite Marañón in support of the enablement of the claims. The Examiner essentially dismisses Marañón on two grounds: that the reference "comes some seven years after the priority date of the instant application, thus, it cannot be used to establish the enablement of the instant application as of its priority date" (Ans. 7), and "the reference employs live antigen-loaded dendritic cells and not the fusion products of the instant claims" (*id*).

Nevertheless, Marañón must considered to the extent it is offered as evidence that the "invention works as claimed" (Reply Br. 4). *See Gould* 822 F.2d at 1078. Moreover, while it is true that the reference discloses dendritic cells co-cultured, rather than fused with HIV-infected cells, we agree with Appellants that its disclosure is relevant to the claimed invention.

Specifically, Appellants contend that Marañón "demonstrates that an APC, a dendritic cell, that expresses viral antigen could be used to eradicate virus" (*id.*). As discussed above, Marañón demonstrates that dendritic cells co-cultured with live, HIV infected $CD4^+$ T cells process and present HIV antigens efficiently, and suggests that "this HIV antigen presentation pathway could be exploited to eradicate latently infected reservoirs" (**FF11**). Also discussed above, the present Specification demonstrates that dendritic cell-tumor cell fusions and dendritic cells co-cultured with tumor cells are comparable in their ability to induce tumor-specific CTLs and protective anti-tumor immunity (**FF7**, **8**). The Examiner has not provided a reasonable explanation for doubting that dendritic cells fused with virally-infected cells would not similarly process and present HIV antigens in a manner comparable to Marañón's co-cultured dendritic cells.

Finally, to the extent the Examiner asserts that the Specification must demonstrate "effective anti-virally-infected cell immunity" in vivo (Ans. 4), we note that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Brana*, 51 F.3d at 1568. The evidence offered by the Examiner does not support his conclusion that the claimed invention had not reached "the stage at which an invention in this field becomes useful" (*id.*) at the time of filing. We conclude that the Examiner has not met his initial burden of establishing that the Specification would not have enabled one of skill in the art to use the claimed hybridoma.

CONCLUSIONS OF LAW

The Examiner has not met his initial burden of setting forth a reasonable explanation as to why it would have required undue experimentation for one skilled in the art to make and use a hybridoma comprising an antigen presenting cell fused to a virally-infected cell.

The rejection of claims 1, 2, and 4-12 under 35 U.S.C. § 112, first paragraph for lack of enablement is reversed.

REVERSED

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007